REMARKS

Entry of the foregoing and reexamination and reconsideration of the above-identified application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112 are respectfully requested. Claims 22, 25-27, 30-33, 83, 86, 88, 91, 93, 94, and 105 were pending, were rejected and remain pending. None have been amended. New claims 106-110 have been added. Support for these claims can be found in the existing claims. These amendments refer to an effervescent agent and amend the amount of same needed to about 30-80% w/w. Drafts of these claims were discussed at the interview.

The undersigned and Mr. Cohen would like to thank the Examiner and her Supervisor for the courtesies extended by them during an interview in the Supervisor's office on May 8, 2008. At that interview, the undersigned, Mr. Cohen and the Examiners discussed the Examiner's positions with regard to the pending claims for further clarification prior to filing this response. No agreement was reached.

The Examiners argued that, despite the characterizations in the previous office action, a rejection which focuses primarily on *Wehling* as the principle reference was perhaps, in their opinion, the strongest rejection and that *Wehling* was combinable with *McCarty*. The remaining references were considered of lesser import.

The Interview

At the interview, the Supervisory Patent Examiner (SPE) expressed some views not expressed in the last official action *per se*. Simply put, the SPE advocated that a rejection starting with *Wehling* was the Patent Office's strongest position and that the Patent Office may ignore any functional language or recited objectives in the claims as relating only to an intended purpose. Paraphrasing, in the SPE's view, "a pill is a pill is a pill." *Wehling* is a pill and, like the claimed invention,

contains an effervescent agent. The Patent Office acknowledged that *Wehling* does not teach a separate pH adjusting substance, but argued that it does allow for an excess of effervescent agent which could effect pH. *Wehling* teaches the use of non-effervescent disintegrants and, while *Wehling* also does not teach fentanyl, the Patent Office noted that it does teach analgesics. And what was missing, according to the Examiner and SPE, could be found in the other cited art. This is a significant condensation of the conversation at the interview and the SPE or Examiner should feel free to supplement or correct it — however, the undersigned believes that this is an accurate summary of the conversation.

To be clear, Applicants do not agree with this position. Applicants do not agree that all of the recitations in the claims are merely functional or related only to intended use and that, in all events, functional or intended use language is not entitled to weight. And as will be demonstrated herein, the case law supports Applicants. Moreover, the Patent Office has itself relied upon the intended use recited in *McCarty*, proposing to combine it with *Wehling* for the former's teachings of buccal administration and fentanyl. The Patent Office's own actions undercut its argument. Finally, Applicants do not believe that it is legally correct or technically accurate to equate, as the Patent Office has done, the possibility of excess effervescent agent to a claim requirement of a pH adjusting substance. Nor do Applicants agree that one is free to ignore the requirement of the claims that there be not only enough effervescent agent present to facilitate disintegration, but also to facilitate transmucosal administration.

Functional Recitations and Intended Uses

Start with a balanced application of the SPG's premise — if Applicants cannot resort to functional language or language relating to the use of the tablet in distinguishing

over the art, then the Patent Office should be similarly restricted. Thus, for example, the Patent Office could not look to *McCarty* for a teaching of a buccal tablet. And the problems with the Patent Office's theory only start there. Why, based on *Wehling*, would one look to deliver fentanyl? Although fentanyl was a known analgesic, why would *Wehling* look to deliver, of all analgesics, fentanyl?

A review of the electronic version of the "Orange Book" available at www.usfda.gov on May 16, 2008 showed no traditional oral delivery of fentanyl. There were two oral transmucosal products (both from Cephalon — the assignee, CIMA, is a division of Cephalon) and the rest were either transdermal or injectable. This real-world information suggests that a swallowable tablet of fentanyl might not be practical. It might be the result of a first pass metabolism issue: an issue with T_{max} — people in the type of pain that fentanyl is indicated for generally cannot wait around for relief to kick in; or it might be that fentanyl is poorly absorbed from this delivery route. In any event, this review of approved commercial products points to a significant problem with the "a pill is a pill is a pill" approach — some actives may not work, or work well enough, in all types of administration platforms. This issue is further penetrated by the fact that *Streisand* 1995 and *McCarty* (the secondary or dictionary references) both teach fentanyl delivery only by a buccal route. Based on this information and these references, why would one suppose that fentanyl could or should be administered by being swallowed, as in the method and tablets taught by *Wehling*?

Consider further, an ALKA-SELTZER tablet. This product has been around for many, many years and is clearly prior art to the current application — and to *Wehling*, for that matter. ALKA-SELTZER tablets are generally too big to be placed in the mouth. There is so much effervescent reaction that it would be difficult, and likely painful, to keep such a tablet in ones

mouth while it dissolves/disintegrates. And, while, like *Wehling*, the active contained within it is intended to be swallowed, in the case of ALKA-SELTZER, this is only bearable after it has been dissolved in water. The tablet itself is clearly not intended to be placed directly in the mouth. But putting aside the very issues in question here, it is a pill and in the view of the Office "a pill is a pill is a pill."

Indeed, without consideration of the intended use or delivery method for a pill, its ingredients — considered in that context, and the active to be administered, no effervescent tablets should have been patentable, including *Wehling*, after ALKA-SELTZER. And even ALKA-SELTZER would not be patentable since effervescent dosage forms were known long before that. *See* GB 0003160, which issued in October **1872**!

In the undersigned's experience, the patent rules and laws are often very practical and it is for the very reasons discussed above that a blanket proposition that anything which could be considered functional or relating to intended use can be ignored is not the law. M.P.E.P. § 2173.05(g) notes that a functional limitation is an attempt to define something by what it does, rather than what it is. Applicants submit that that is not an accurate characterization of every one of the limitations ignored by the Patent Office. As to others, the same section of the M.P.E.P. goes on to note that "[t]here is nothing inherently wrong with defining some part of an invention in functional terms."

And the United States Court of Appeals for the Federal Circuit agrees. In *Union Oil Co. v. Atlantic Richfield Co.*, 54 U.S.P.Q.2d 1227, 1231 (Fed. Cir. 2000), the court affirmed a lower court's interpretation of a claim which contained the phrase "[a]n unleaded gasoline *suitable for* combustion in an automotive engine" was a composition, and not a method. *Id.* (emphasis added). Furthermore, the "district court correctly excluded from claim scope a broader class of petroleum

formulations such as aviation fuels or racing fuels." *Id.* "The district court read each claim in light of the specification, and concluded that the claims cover 'fuels that will *regularly* be used in autos, not that conceivably could be.'" *Id.* (emphasis in original). Thus functional language cannot be ignored and can limit the scope of a claim. The "suitable for" language accepted and properly interpreted by the Federal Circuit is found in the instant claims, but has been improperly discounted by the Office.

And finally, as briefly mentioned previously in regard to the official action, the Patent Office itself looked to combine *McCarty* as a secondary reference with *Wehling* for the former's teaching of fentanyl and its intended use of buccal administration. Accordingly, and with all due respect, practicality, the law, and the rejection all suggest that the Patent Office's argument is not sustainable. Accordingly, Applicants submit that these types of limitations must be considered and are important to the patentability of the invention.

Wehling in View of McCarty

Despite the fact that the last office action started with a rejection based on *McCarty* in view of *Wehling*, in view of the SPE's opinion on the relative merits of the rejections as expressed at the interview, Applicants will first address the rejection of *Wehling* in view of *McCarty*.

Wehling is not just directed to a tablet intended to be swallowed, but indeed, it is a reference which all but precludes buccal administration. The entire teaching of *Wehling* is the creation of a tablet which will disintegrate rapidly in the mouth in a way which prevents the patient from tasting the objectionable tasting active ingredient within. It provides not only effervescent agents but non-effervescent disintegrants to ensure that the tablet destroys itself quickly so that it can be

swallowed, even without water. It teaches that the effervescent agent helps provide a pleasant organoleptic sensation, furthering taste masking, and generates saliva to aid in swallowing. It even teaches the use of coatings and microparticles in preferred embodiments — structures to further prevent in-mouth exposure. All of this tablet design and structure is put to but one end — reducing the amount of time that an active dwells in the mouth so that it is not tasted.

Manifestly, *Wehling* does not teach a buccal or other type of transmucosal tablet. Buccal administration would be antithetical. It also does not teach fentanyl. This is possibly no surprise as fentanyl does not appear to be a desirable active for a swallowed dosage form based, *inter alia*, on the commercial incarnates of fentanyl-containing dosage forms and the fact that both *Streisand* 1995 and *McCarty* address fentanyl delivery only in terms of transmucosal administration.

But these are not the only deficiencies between *Wehling* and the claims. *Wehling* also does not teach a pH adjusting substance. While the Patent Office has pointed out that *Wehling* teaches the possible use of an excess of an effervescent agent, that is in no measure the same thing. *Wehling* teaches that an excess of acid or base may be present to assist in enhancing taste masking and/or performance, both of which, in the context of the specification and claims of *Wehling*, mean its ability to rapidly disintegrate and taste mask. It does not teach the need or desirability of selecting a particular material such that it can influence the dissolution and absorption rate of a particular active via an oral mucosal surface.

And, while *Wehling* does teach the use of an effervescent agent, it just as clearly does so <u>only</u> in the context of disintegration and taste masking. Indeed, in the Disclosure of the Invention section, *Wehling* states: "The effervescent disintegration agent is present in an amount effective to aid in disintegration of the tablet, as to provide a distinct sensation

of effervescence when the tablet is placed in the mouth of a patient." (WO 91/04757, at 4 ll.4-8.) Nowhere in *Wehling* is there a recognition of the need to use not only enough effervescent for disintegration, but, in addition, enough effervescent material to aid in transmucosal delivery — again no surprise given the objective of *Wehling*. And this is not a functional recitation, it is a statement of the amount of an ingredient needed.

Thus, there is no shortage of things that *Wehling* does not have or teach when compared to the claimed invention. To plug those numerous gaps, the Patent Office turns to *McCarty* which teaches both fentanyl and buccal delivery. But are these references properly combinable? Applicants are of the opinion that the answer is no.

Even after *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007), there must be objective reasons why and how two references are combinable. And references must be considered for not only their teachings that support a combination, but all of their teachings, including those which would counsel away from that combination. (*See* M.P.E.P. § 2141.02 and *W.L. CORE & ASSOC., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1550 (Fed. Cir. 1983) ("the district court erred in . . . disregarding disclosures in the references that diverge from and teach away from the invention at hand.")

Why would *Wehling*, or more correctly, one looking to create a tablet based on *Wehling*, look to a reference that counsels buccal delivery? *Wehling*'s complete disclosure is directed to getting the active out of the mouth, without being tasted, as quickly as possible. That means, as noted above, it must prevent the active from coming in contact with the internal surfaces of the mouth for any extended length of time. It does this by disintegrating rapidly so the tablet can be swallowed, even without water to wash it down. It does this by ensuring

that the solution or suspension of the active that is created can be rapidly swallowed.

Why would *McCarty* be combinable with *Wehling* as *McCarty* teaches that the active should not be swallowed at all — that it should be retained in the mouth for as long as it takes to get the active across the oral mucosa? That would necessitate the complete abandonment of the entire purpose of *Wehling* and no rational view of obviousness would require that. (*See* M.P.E.P. § 2143.001 ("proposed modification cannot render the prior art unsatisfactory for its intended purpose or change the principle of operation of a reference.") And why would *Wehling* look to deliver fentanyl, a drug which, at least commercially and based on *McCarty* and *Streisand* 1995, does not appear to be a good candidate for a traditional oral route of administration? Indeed, the fact that fentanyl is mentioned in *McCarty* for buccal administration might also suggest to the art that fentanyl is not a bad tasting drug — one in need of *Wehling*'s special and unique approach to taste masking.

Moreover, looking at the totality of *McCarty*, as the Patent Office is charged with doing, one cannot avoid its teaching that to accomplish its goal of buccal administration, one must formulate with 90% or more of a limited number of highly water soluble excipients. In fact, in the examples, the lowest amount of these excipients, sugars all, is greater than 96%. There can be no disputing the role of the sugar in *McCarty* as the only other required ingredients are a small amount of lubricant and the active.

Yet, according to the claimed invention, there must be at least 20% by weight of the effervescent agent, and in newly added claims 106-110, at least 30%. One simply cannot amend *Wehling* by combination with *McCarty* in a way which permits the present invention. To do so would destroy <u>both</u> *Wehling*'s objective of taste masking and *McCarty*'s teaching of the need for at least 90% of a critical ingredient. Not only does this

underscore the lack of an objective rationale for the combination, it also illustrates that the combination, even if possible, could not produce the present invention.

And even if this combination was proper, which for the reasons discussed above is not the case, it would not resolve all of the deficiencies of *Wehling*. There is no teaching of the use of enough effervescent agent to promote transmucosal absorption. And then there is the matter of the pH adjusting substance.

Streisand 1995 is cited for its teaching that fentanyl penetration from a solution across a membrane is made better by basic conditions. This is no surprise as *Streisand* 1995 merely confirms the Henderson-Hasselbach (H-H) effect that's disclosed in the present application (starting at page 5 line 27), and provides an invitation to conduct further experiments.

And, of course, many of the same issues which plague the proposed combination of *Wehling* and *McCarty* apply to the combination with *Streisand* 1995 as well. The only way that the *Streisand* 1995 observation of the membrane behavior of fentanyl under basic conditions is relevant is if one were to ignore the very purpose of *Wehling*, namely taste masking. As was the case with *McCarty*, *Streisand* 1995 does nothing to explain why *Wehling* would or should abandon its objective of taste masking a drug to be swallowed or why one would look to *Wehling* for delivery of fentanyl in a way that precludes swallowing.

Even if one were going to ignore these problems with the combination, *Streisand* 1995 is a very unlikely candidate. *Streisand* 1995 is not only incompatible because it requires that the active remain in the mouth, but also because it is a liquid. *Wehling* requires an effervescent agent and that is not possible in a liquid.

The importance of this latter point can not be emphasized enough. *Wehling* notes that their "water activated materials must be kept in a generally anhydrous state . . . since exposure

to water will prematurely disintegrate the tablet." (WO 91/04757, at 11 11.34-37) These statements were made in describing the effervescent agents. One would not reasonably look to *Streisand* 1995 at all. Moreover, the teaching of *Streisand* 1995 is not, as the Patent Office posits, that a base will help the transmission of fentanyl, it is that a higher pH, a base, in a solution including fentanyl, a solution which renders an effervescent agent impossible, might help transmission of fentanyl when that solution is left in contact with the membrane for about an hour. "Might" because *Streisand* 1995 questions the practical significance of their work: "Can the results of our study be related to clinical practice?" (P.5 last col.) In other words, there's nothing in *Streisand* 1995 to suggest that the results can be translated into a practical effect and certainly there's nothing to suggest combining its teachings with the use of an effervescent couple as taught by the present invention.

And none of the references teach the use of sufficient disintegrant and/or sufficient effervescent material to increase transmission of the active across the oral mucosa. The primary reference *Wehling* does not want such transmission and the secondary and tertiary references *McCarty* and *Streisand*, teach nothing about the use of effervescents at all.

With all due respect, *Streisand* 1995 and *McCarty* bring into sharp relief the real basis of the rejection — an impermissible hindsight reconstruction of the invention using Applicant's invention as a map or shopping list. There is no reason to combine the references other than the fact that *Wehling* superficially discloses the possibility of a number of the claimed elements, and the others contain the missing elements. The fact that these references could not be combined without ignoring the very objective of the primary reference, and that the combination would be impossible without either ignoring the

critical amount of sugar in one teaching and the use of a liquid in the other is proof of Applicants' position.

McCarty in View of Wehling

McCarty in view of *Wehling*, the original primary rejection, is no better. *McCarty* is missing almost everything claimed. Applicants have noted the deficiencies of *McCarty* before. *See* table at page 8 of the Amendment of September 12, 2007.[1] There is no teaching of an effervescent agent at all, let alone an amount which is sufficient to aid in transmucosal delivery. There is no teaching of a pH adjusting substance, let alone a base. There is no teaching of a non-effervescent disintegration agent other than very specific sugars. Indeed, as to the latter, *McCarty* actually notes that other buccal formulations were possible using disintegrants, but very pointedly declined to use them. (*See McCarty* col.1 ll.51 *et seq.*) In short, about all that *McCarty* teaches is that some drugs, including fentanyl, can be administered buccally.

Accordingly, *McCarty* provides almost no teaching relevant to the present invention. The Patent Office, however, takes a position that a person of ordinary skill in the art would look to *Wehling* and other references potentially to modify those teachings. Why? Where is the objective teaching, suggestion, motivation or other reason apparent from the art or otherwise for looking beyond the express teachings of *McCarty*? Note that *KSR* did not eliminate the need for some objectively reasonable basis for the combination.

> The TSM test, flexibly applied, merely assures that the obviousness test proceeds on the basis of evidence — teachings, suggestions (a tellingly broad term), or motivations (an equally broad term) — that arise before the time of invention as the statute requires. As *KSR* requires, those teachings, suggestions, or motivations need not always be written references but

[1] All of Applicants' prior arguments in the Amendment of September 12, 2007, are incorporated by reference.

> may be found within the knowledge and creativity of ordinarily skilled artisans.

Ortho-McNeil Pharma. Inc. v. Mylan Labs. Inc., 86 U.S.P.Q.2d 1196, 1202 (Fed. Cir. 2008).

McCarty suggests that it is successful. So why would one look to change it? And if one wanted to improve its performance, why would *McCarty* suppose that effervescent agents would do the trick; not just effervescent agents — but an amount of effervescent agent (20% or more) making it impossible to meet its own pivotal requirement for the use of 90% or more of specified sugars? The combination of *McCarty* in view of *Wehling* proposed by the Patent Office, therefore, destroys the only instrumentality recognized in the primary reference of achieving buccal administration — the amount of sugar used.

And lest one forget, *McCarty* is designed to avoiding swallowing. *Wehling* is a tablet that is designed to provide taste masking and promote swallowing. Indeed, that is its central tenet. It seeks to prevent the very thing essential in *McCarty*, namely retention in the mouth. In fact, in preferred embodiments, *Wehling* actually teaches coating the active for taste masking purposes affirmatively preventing its dissolution in the mouth. There is no reason apparent from either *Wehling* or from *McCarty* or, for that matter, from anything else of record, as to why one would seek to combine these references.

This is not a likely combination. This is not a probable combination. This is not a reasonable combination. This is not a possible combination. Thus, the rejection is not proper.

Again, it is clear that the Patent Office has engaged in an impermissible hindsight reconstruction of the invention. The principle reference, *McCarty*, knew about the possibility of using conventional disintegrants in buccal tablets. Yet it chose not to do so, going instead for the highly unusual approach of including between 90 and 99% of a rapidly dissolvable sugar. *McCarty* also differentiated buccal

administration from tablets designed to be swallowed. Yet, for reasons that are not apparent from the record, one of ordinary skill in the art would: (1) ignore both of these facts and seek out the use of disintegrants, both conventional, and effervescent; (2) do so — not from a teaching relative to another buccal tablet, but from a tablet designed to be swallowed; and (3) do so in amounts which can not possibly be reconciled with the critical feature of the primary reference, the amount of sugar required. Clearly the Patent Office has done nothing more than find the necessary elements from discrete, and distinct, references in the overall pharmaceutical industry. And, for no apparent reason of record, suggested their combination. That is impermissible hindsight.

Streisand 1995 is no more of a help in this rejection than in the last. *Streisand* 1995 is a liquid formulation. Yet *McCarty* teaches a solid formulation produced from over 90% of a highly water soluble excipient. Those two formulations clearly cannot co-exist. And *Wehling* teaches the use of an effervescent agent. It also teaches that an effervescent agent must remain anhydrous. Obviously, when wet, the effervescent agents evolve gas and are consumed. Yet, in an effort to find the myriad of missing elements of the principle reference, the Patent Office ignores these teachings, and the lack of a reason to look at a liquid and swallowable formulations.

Indeed, the combination with *Streisand* 1995 is contraindicated by its teaching. Ignoring that it is a liquid, and that it is honest enough to admit that it is unsure if its teachings have any applicability at all, *Streisand* 1995's suggestion of improved results using a base must be contrasted with the fact that those results came from exposure of a solution over a large surface area for about an hour. Yet *McCarty* seeks absorption in about 5 minutes or less. (Col.2 ll.51-53.) If *McCarty* was looking for "improved" performance, *Streisand* 1995 might be the last place to look!

Streisand, Anesthesiology (1991) in View of Streisand et al., Anesthesiology (1995) and further in View of Wehling

Streisand 1991 teaches an oral transmucosal fentanyl citrate dosage form which consists of a lozenge with a handle — like a lollipop. It is made by dissolving fentanyl citrate in a sucrose solution that is poured into a mold and allowed to harden. Upon administration, a portion of the fentanyl diffuses across the oral mucosa and the rest is swallowed. The remaining *Streisand* reference (*Streisand* 1995) and *Wehling* have been previously discussed.

With all due respect, this rejection is even more tenuous than the rejection predicated on *McCarty* as the principle reference. Like *McCarty*, the disclosure of the oral transmucosal dosage form of *Streisand* 1991 is of fentanyl and a sugar. Also like *McCarty*, there is no discussion of an effervescent material, let alone enough effervescent material to improve absorption. And there is no disclosure of rapid disintegration of the delivery form, the lozenge, since such disintegration is antithetical to such dissolving delivery. There is no discussion of a pH adjusting substance, let alone a base. And there is no discussion in the official action or in the references as to how such a combination could be accomplished. *Streisand* 1991 talks of buccal administration over a period of 15 minutes, whereas *Streisand* 1995 discusses an exposure of an hour. (*Streisand* 1995, at 760 col.2 l.18; Fig.2.) And how exactly would one combine an effervescent material into a "sucrose solution." (*Streisand* 1991, at 223.) without consuming the effervescent agent? Is there any evidence that an effervescent agent, uniformly distributed in a lozenge and released slowly as the lozenge melts in the patient's mouth over 15 minutes would be of any value whatsoever? Or that a pH adjusting substance, when administered in this fashion, would have the desired result? The answer to all of these questions is no.

There is nothing of record to suggest that this combination is possible and for the very significant, technical reasons discussed above, one would expect that such combinations could not be accomplished. And why, in view of the beneficial results of *Streisand* 1991 would one seek to combine it with *Wehling* in the first place? According to *Streisand* 1991, a lozenge with a stick provided superior results to a solution which was swallowed. Why would one look to a tablet which is designed to be swallowed — which is designed to taste mask and minimize exposure in the mouth — for combination with *Streisand* 1991 whose residence time is 15 minutes and whose results were better than a swallowed liquid dosage form provided? There are simply no reasons of record to make the proposed combination other than in hindsight as discussed above. There is no reasonable expectation of success. Indeed, there was every reason to believe that the physical combination is not possible.

Applicants respectfully submit that the Patent Office's cause is further set back, not advanced, by this proposed rejection.

Norling in view of Wehling

Claims have also been rejected pursuant to 35 U.S.C. § 103 over Norling *et al.*, U.S. Patent No. 5,958,458 ("*Norling*") in view of *Wehling*. Again, Applicants respectfully traverse. Neither *Norling* nor *Wehling* appear to teach transmucosal administration. Indeed, both teach a swallowable dosage form. That alone sufficiently undermines the rejection to render it moot. However, *Norling* further retreats from the presently claimed invention. *Norling* describes coated cores. One central purpose of the design of *Norling* was to produce cores sufficiently rugged enough to withstand the coating process. In this way, *Norling* and *Wehling* are completely consistent and distinct from the present invention. *Wehling* too teaches, as a preferred embodiment, the formation of microparticles which are

coated. Yet there is little that Applicants can think of which so undermines the possibility of transmucosal delivery than a coated active. Coatings, be they for altering the release of the active or for taste masking as in the case of *Wehling*, will delay or even prevent dissolution of the active ingredient contained within. They will, in short, delay or prevent transmucosal administration.

Moreover, even if one were to combine the effervescent material disclosed in accordance with *Wehling*, the teaching of the combination would be that sufficient effervescent material be provided to assist in the rapid disintegration of the dosage form in the mouth so it could be swallowed — not to assist in the transmucosal administration of the coated active of *Norling*. Applicants respectfully submit that this rejection is even less relevant than the ones that have been discussed previously.

Chen et al. Chinese Pharmaceutials, 1997, 28(3), 129-31, in View of Wehling

Finally, claims have been rejected pursuant to 35 U.S.C. § 103 over *Chen et al.* in view of *Wehling* and further in view of *Streisand* 1995. For the reasons previously discussed in Applicants' Amendment Accompanying RCE filed September 12, 2007, the complete arguments of which, including but not limited to those relating to the combination with *Chen*, are hereby incorporated by reference as if fully set forth herein. Applicants respectfully traverse. The *Chen* reference suffers from many of the deficiencies previously noted. It does not teach the use of an effervescent agent, let alone a sufficient amount to assist in transmucosal administration. It does not teach the use of a pH adjusting substance and specifically a base. Indeed, *Chen* includes a good deal of Carbopol in all of its formulations and acknowledges that Carbopol is an "acidic substrate" and is thus contrary to the requirements of the instant claims. Furthermore, *Chen* does not disclose that any disintegration agent, effervescent or otherwise, should be used

(although three compositions included corn starch, there is no indication why it was used and the preferred composition does not include any).

And for the reasons previously discussed, there is no reason on this record to combine these references (*Chen* and *Wehling*), nor would the combination teach all of the claimed elements; namely, the use of a pH adjusting substance, and an amount of effervescent agent sufficient to assist in transmucosal administration.

Unexpected Results

Finally, Applicants wish to remind the Patent Office of a declaration of Dr. Vikas Agarwal, a Group Leader for Applicants, accompanying the Amendment and Response to official action of April 19, 2006. The data therein showed that the claimed combination of an effervescent agent and a pH adjusting substance in an otherwise identical formulation was superior to the use of either a pH adjusting substance or an effervescent agent alone. Compositions falling within the scope of the claims resulted in significantly superior performance. Indeed, permeability values obtained were more than 400% greater than the next closest formulation using only one of the two required components.

Nothing of record teaches the types of advantages which could inure from the use of both a pH adjusting substance and an effervescent agent in terms of transmucosal permeability. We note that the formulations tested included a combination in an otherwise identical formulation that included magnesium stearate, mannitol, and sodium starch glycolate. This formulation is the subject of other pending applications already identified in this case, including, *inter alia*, U.S. Patent Application Nos. 11/026,132, 11/027,353 and 11/026,759. However, the remainder of the formulation should not be relevant to the questions involved in this case, namely the discovery

that the combination of a pH adjusting substance and an effervescent agent is superior to the use of either alone in an otherwise identical formulation.

Double Patenting

Finally, Applicants note various provisional obviousness type double patenting rejections including over claims 1-30 of co-pending application nos. 11/026,132, 11/027,353, and 11/511,098. These are provisional rejections. When allowable subject matter is found in this case, as Applicants respectfully submit should happen, Applicants will consider the status of the identified applications. If appropriate, argument as to why the presently claimed invention is unobvious over claims of those applications (more correctly any patent previously issuing therefrom) and/or a terminal disclaimer will be considered as appropriate at that time.

As it is believed that all of the rejections set forth in the official action have been fully met, favorable reconsideration and allowance are earnestly solicited.

If, however, for any reason the Examiner does not believe that such action can be taken at this time, it is respectfully requested that he/she telephone Applicants' attorney at (908) 654-5000 in order to overcome any additional objections which he might have.

If there are any additional charges in connection with this requested amendment, the Examiner is authorized to charge Deposit Account No. 12-1095 therefor.

Dated: May 23, 2008

Respectfully submitted,

By _____

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